REVIEW ARTICLE

Advances in the treatment of mild asthma: recent evidence

Paul M. O'Byrne[1], Filip Mejza[2]

1 Firestone Institute for Respiratory Health, St. Joseph's Healthcare and Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada
2 Centre for Evidence Based Medicine, II Department of Internal Medicine, Jagiellonian University Medical College, Kraków, Poland

KEY WORDS

inhaled corticosteroids, management, mild asthma

ABSTRACT

Asthma affects about 300 million individuals worldwide. Although most patients have mild disease, the majority of them do not have good control and are at risk of exacerbations. Poor compliance with regular maintenance treatment is a considerable problem and is believed to be the main reason for poor control in asthma. In patients with moderate to severe asthma, maintenance and as-needed treatment with one inhaler containing an inhaled corticosteroid (ICS) and the long-acting inhaled β_2-agonist formoterol has been proved effective in reducing the risk of severe exacerbations. Recently, the results of 2 large double-blind randomized trials assessing the use of as-needed budesonide/formoterol in patients with mild asthma, who had indications for a regular controller treatment, were published. In comparison with as-needed terbutaline treatment, as-needed budesonide/formoterol treatment improved symptom control and reduced the risk of exacerbations. In comparison with regular ICS treatment, exacerbation rates were similar, but regular treatment schedule was associated with better asthma control (despite a higher cumulative ICS dose). The results of these trials have shown that as-needed budesonide/formoterol therapy has acceptable efficacy in mild asthma and may be viewed as a therapeutic option for these patients. As-needed treatment may be preferred by patients who fear the side effects of ICS treatment or by those who experience difficulty in following a fixed-dose regimen. Patients with mild asthma wishing to achieve optimal asthma control may prefer regular maintenance treatment with an ICS.

Correspondence to:
Filip Mejza, MD, PhD,
Centre for Evidence Based Medicine,
II Department of Internal Medicine,
Jagiellonian University Medical
College, ul. Skawińska 8,
31-066 Kraków, Poland,
phone: +48 12 430 52 66,
email: filipmejza@hotmail.com
Received: September 14, 2018.
Accepted: September 15, 2018.
Published online: September 28, 2018.
Conflict of interest: see at the end of text.
Pol Arch Intern Med. 2018;
128 (9): 545-549
doi:10.20452/pamw.4341

Introduction The number of patients with asthma exceeds 300 million globally.[1] Asthma constitutes a significant burden to patients and health care systems worldwide. According to Global Burden of Disease Study data in 2015, 26.2 million disability-adjusted life years were lost due to asthma and as much as 400 000 patients died of asthma.[2] The data on asthma burden are concordant with those demonstrating that the goals of treatment (including symptom control and prevention of exacerbations) are not achieved in a significant proportion of patients,[3,4] even though most patients (50%–75%) have mild disease.[5] Currently, asthma severity classification is based on the level of treatment intensity needed to control the symptoms and should be assessed after several months of controller treatment (TABLE 1).[6] Mild asthma is defined as the disease that is controlled with as-needed reliever medication alone (Step 1) or with regular low-intensity treatment (Step 2). This encompasses patients with sporadic asthma and those with more frequent symptoms.

Regardless of asthma severity level airway inflammation is always present.[7] Currently, regular controller treatment is indicated in patients requiring inhaled reliever therapy more than twice per week, or any nocturnal symptoms, or limitation of activities due to asthma, or risk factors for asthma exacerbations.[6] The preferred therapeutic option in this group is the regular use of low-dose inhaled corticosteroids (ICSs). ICSs are the most effective agents for controlling airway inflammation and modifying the course of the disease, regardless of its severity.[5] Another possibility of low-intensity controller treatment is the use of leukotriene receptor antagonists, which are less effective than ICSs, but may be chosen by patients with concerns about side effects of ICS treatment.

TABLE 1 Levels of intensity of asthma treatment (based on Global Initiative for Asthma [GINA] Guidelines, modified)[6]

Step	Preferred regular (controller) treatment	Other option(s)	As-needed treatment (reliever)
1	None	Consider low-dose ICS	SABA
2	Low-dose ICS	LTRA	SABA
3	Low-dose ICS/LABA	Medium/high-dose ICS Low-dose ICS + LTRA	SABA Low-dose ICS/formoterol
4	Medium/high-dose ICS/LABA	Medium/high-dose ICS + tiotropium Medium/high-dose ICS + LTRA	SABA Low-dose ICS/formoterol
5	Refer for specialist care, add tiotropium, anti-IgE, anti–IL-5	Add low-dose OCS	SABA Low-dose ICS/formoterol

Abbreviations: anti-IgE, anti–immunoglobulin E; anti–IL-5, anti–interleukin-5; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2-agonist

Data from multiple clinical trials indicate that ICS treatment leads to improved symptom control and a significant reduction in the risk of exacerbations[8-11] as well as a reduction of airway inflammation.[12] Unfortunately, according to real-life data, asthma is uncontrolled in more than 50% of patients,[4,13] and most of them are at risk of exacerbations.[14,15] Importantly, this is also true for the population with mild asthma, with the high proportion of subjects with uncontrolled asthma and the rate of severe exacerbations reported to range from 0.12 to 0.77 per patient-year.[16] One of the most important reasons for discrepancy between real-life observations and the results from clinical trials is the lack of patients' compliance with maintenance treatment.[17] A population-based survey has reported that only a minority of patients diagnosed with asthma received adequate treatment.[18] This may result from different socioeconomic factors, with the lack of compliance being clearly the important one, as only about 50% of patients are reported to adhere to treatment recommendations.[19] According to pharmacy data, the amount of asthma medication prescriptions filled was sufficient only for about 22% of the days of the year, and only less than 10% of patients continued treatment for longer than 1 year.[20] The mean adherence rate to ICS treatment ranges from 22% to 63%.[21] About one-fourth of asthma exacerbations may be related to nonadherence to ICS treatment.[22] Poor compliance has been reported in patients with asthma across all levels of disease severity: from mild to severe asthma.[23,24] Moreover, some patients use controllers when symptoms are present, but stop regular treatment on achieving disease control, which leads to clinical deterioration. Finally, it has to be remembered still than even patients with mild asthma adequately treated with ICS are at risk for severe exacerbations: in a large randomized clinical trial (RCT) lasting 3 years, 3.2% of ICS-treated patients with mild asthma had severe asthma exacerbation (compared with 5.5% of those receiving placebo).[25]

Single-inhaler maintenance and rescue therapy

The availability of inhalers containing both an ICS and a long-acting β_2-agonist (LABA) with a rapid onset of action (formoterol) led to the concept of symptom-driven asthma treatment. In this treatment approach, patients are advised to use only one inhaler containing both an ICS and a rapid-acting LABA as maintenance (twice daily), as well as for as-needed treatment when symptoms occur. Such an approach is sometimes referred to as MART (maintenance and reliever therapy). This approach has some advantages, including: 1) ICS dose is increased when symptoms are present and adjusted to symptom severity; 2) the inhaler contains a rapid-acting β_2-agonist, so the effect of inhalation is immediately felt by the patient; and 3) the patient has the sense of a more active participation in therapy. The 2 latter benefits may potentially improve adherence to therapy, although this has not been formally studied.

The above approach to treatment has been studied in a number of RCTs, done mainly in patients with moderate to severe asthma.[26-33] MART was more effective in terms of reducing the risk of exacerbations when compared with the regular use of a higher ICS dose, or a combination of ICS and LABA. A reduction in the risk of exacerbations was also reported in a Cochrane meta-analyses by Kew et al,[34] who pooled the results of 4 studies comparing MART with LABA and ICS combination treatment (odds ratio [OR], 0.72; 95% CI, 0.57–0.90 for events requiring hospitalization or emergency department visit), and by Cates and Karner,[35] who analyzed 8 studies which used the "current best practice" as the comparator (OR, 0.83; 95% CI, 0.70–0.98 for exacerbations requiring oral corticosteroid course). In both meta-analyses, MART was associated with a lower total dose of ICS.[34,35] Consequently, the current guidelines allow a maintenance and reliever therapy with low-dose ICS/formoterol as an option in patients requiring Steps 3 to 5 treatment.[6]

The approach based on symptom-driven ICS dosing has now been studied in patients with milder asthma. A 6-month RCT showed that as-needed treatment with beclomethasone (250 μg) and albuterol in a single inhaler had similar effects to regular treatment with beclomethasone (250 μg twice daily alone or 250 μg twice daily in a single inhaler with albuterol).[36] There were nonsignificant differences in lung function, daytime and nighttime symptom scores, as well as rescue medication use between the as-needed group and patients on regular beclomethasone treatment (or beclomethasone with albuterol). The number of exacerbations was similar in the as-needed and regular beclomethasone groups and lower compared with the regular beclomethasone and albuterol group. Another trial randomized patients with

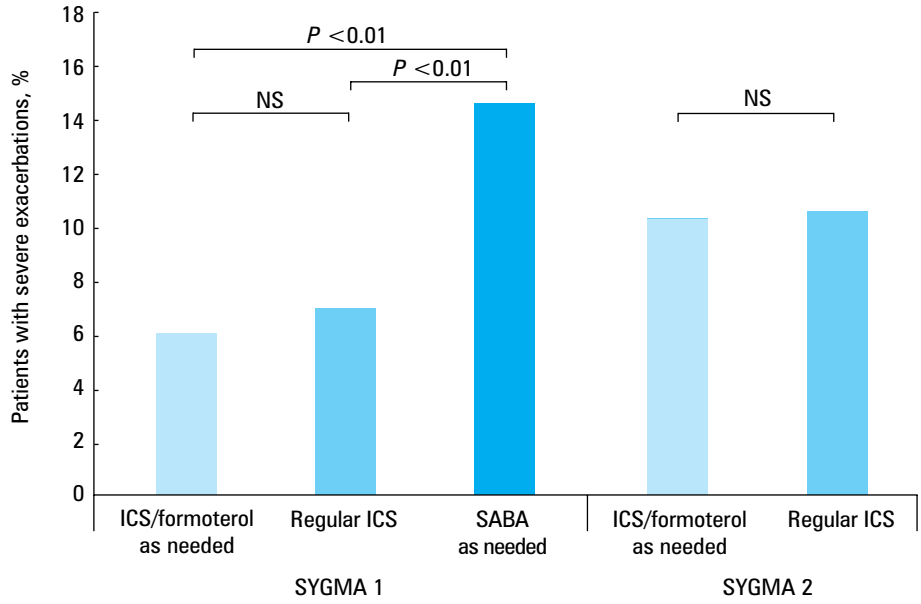

FIGURE 1 Proportion of patients with severe exacerbations in SYGMA 1 and SYGMA 2 trials
Abbreviations: NS, non-significant; others, see **TABLE 1**

mild and moderate asthma to a treatment with an ICS inhaled each time when a rescue inhaler was used or to regular treatment adjusted as per guidelines or based on exhaled nitric oxide levels.[37] The symptoms-based ICS dosing was similarly effective as regular ICS therapy in the 2 other trial groups (similar time to first treatment failure, treatment failure rates, symptom scores, or exacerbation rates). In both trials, cumulative doses of an ICS were lower in patients allocated to the symptom-driven treatment arm.

Recent data on intermittent inhaled corticosteroid dosing in mild asthma Recently, the results of 2 large double-blind RCTs, SYGMA 1 (Symbicort Given as Needed in Mild Asthma 1) and SYGMA 2 (Symbicort Given as Needed in Mild Asthma 2), assessing as-needed use of ICS/LABA in mild asthma, were published.[38,39] The studies included children aged at least 12 years and adults with mild asthma, who had indications for regular ICS treatment. Each study lasted 52 weeks and included about 4000 participants. Approximately half of the patients in both trials had uncontrolled asthma while using only as-needed short-acting inhaled β_2-agonist (SABAs), whereas the other half had well-controlled asthma using low-dose ICS. In SYGMA 1, participants were randomized to one of the 3 arms: 1) the SABA (terbutaline) used as needed, 2) budesonide and formoterol in one inhaler (200 µg + 6 µg) used as needed, or 3) twice-daily budesonide (200 µg) and terbutaline as needed. In the first 2 arms, a matched placebo was used twice daily.[38] In SYGMA 2, patients were randomly assigned to twice-daily placebo with budesonide and formoterol inhaler (200 µg + 6 µg) used as needed or twice-daily budesonide (200 µg) with terbutaline used as needed.[39]

In SYGMA 1, in comparison with as-needed terbutaline treatment, as-needed ICS/LABA treatment improved symptom control and reduced exacerbation risk. As-needed budesonide/formoterol increased the proportion of weeks with well-controlled asthma (OR, 1.14; 95% CI, 1.00–1.30; $P = 0.046$) and significantly reduced the annual rate of severe exacerbations (rate ratio, 0.36; 95% CI, 0.27–0.49).

The comparison with regular budesonide treatment yielded similar results in both trials despite some differences in study designs. In SYGMA 1, the rates and time to the first severe and moderate to severe exacerbations were among secondary outcomes, and they did not differ significantly between regular ICS and as-needed ICS/LABA treatment. In SYGMA 2, the annual rate of severe exacerbations was the primary outcome, and the trial was able to confirm noninferiority of as-needed ICS/LABA compared with regular budesonide treatment. Neither trial found a difference in the number of severe exacerbations between as-needed ICS/formoterol treatment and regular ICS treatment (FIGURE 1).

These studies used different methods to assess asthma control, but in both studies as-needed budesonide/formoterol was inferior to regular budesonide treatment. In SYGMA 1, the number of weeks with well-controlled asthma was the primary outcome, and control was assessed based on the use of as-needed medication, data from an electronic diary (including daytime symptom score, nighttime awakening and morning peak expiratory flow), and data on an additional use of inhaled or oral corticosteroids. In SYGMA 2, the percentage of reliever-free days and the Asthma Control Questionnaire-5 (ACQ-5) score were among the secondary endpoints. Compared with as-needed ICS/LABA use in patients on regular ICS treatment, the proportion of weeks with well-controlled asthma was significantly higher in the SYGMA 1 trial (44.4% vs 34.4%), whereas in SYGMA 2, the change in ACQ-5 score was larger by 0.11 points (95% CI, 0.07–0.15). Similarly, in both trials, regular ICS treatment led to a greater increase in lung function compared with as-needed combined budesonide/formoterol treatment. On the other hand, the ICS doses in as-needed budesonide/formoterol groups were

TABLE 2 Treatment options for mild asthma

Treatment option	Comments
Low-dose ICS	Current first-line treatment; robust evidence of effectiveness. May be preferred in patients willing to have optimal asthma control and prevent any asthma-related lung function decline. Side effects are mild and local (hoarseness, oral candidiasis).
Low-dose ICS + formoterol as needed	Alternative treatment; good quality evidence for effectiveness. Compared with regular ICS: similar reduction in exacerbation risk, worse symptom control and lung function. May be preferred in patients with low adherence to treatment or afraid of side effects. Lower cumulative ICS dose.
LTRA	Alternative treatment; less effective than ICSs. May be preferred in patients with concomitant allergic rhinitis or those afraid of side effects (or experiencing such effects).
Theophylline	Alternative treatment mentioned in the GINA guidelines; less effective than ICS. Should not be used in settings when inhaled drugs are available due to the risk of serious side effects

Abbreviations: GINA, Global Initiative for Asthma; others, see TABLE 1

significantly lower than those in the budesonide maintenance groups both in SYGMA 1 (57 μg and 340 μg, respectively) and in SYGMA 2 (66 μg and 267 μg, respectively).

Conclusions The results of the SYGMA 1 and SYGMA 2 trials are consistent with previous studies conducted in patients with moderate to severe asthma. Therefore, there is now sound evidence that as-needed therapy with ICS and rapid-acting LABA is as effective in preventing exacerbations in patients with mild asthma as regular ICS dosing. The data also confirm that this therapy leads to better asthma control compared with as-needed use of short-acting β_2-agonists, but inferior when compared with regular ICS dosing.

These findings have some practical implications. The currently preferred therapeutic option in patients with mild asthma and indications for regular controller is regular low-dose ICS treatment. This is still applicable in view of SYGMA 1 and 2 results because as-needed budesonide/formoterol treatment was inferior to regular ICS in terms of asthma control. However, as-needed budesonide/formoterol emerged as an alternative treatment because it is effective in preventing severe asthma exacerbations, which are a serious threat also in patients with mild asthma. This approach has 2 additional advantages. First, a similar reduction in the rate of exacerbations is achieved with a much lower ICS dose, which may alleviate concerns of patients about the side effects of ICSs. Second, as-needed (symptom-driven) dosing may be a practical solution in patients with poor adherence. It should be noted that adherence was high in both trials (about 79% and 63% in SYGMA 1 and SYGMA 2, respectively), and exceeded the rates typically observed in the real-life setting. An important consideration, however, is that regular ICS treatment resulted in better lung function and asthma control, although the differences observed in the trials did not exceed the clinically important difference for either forced expiratory volume in 1 second or ACQ-5.

These studies suggest that there is yet another therapeutic option for mild asthma, which allows clinicians to better tailor treatment to the individual patient's needs (TABLE 2). This new regimen may appeal to patients who are concerned about the side effects of ICS treatment (as the dose is much lower than in regular treatment), or to those who experience difficulty in following the fixed-dose regimen. On the other hand, patients willing to achieve optimal asthma control may choose regular ICS treatment. The art of medicine is the art of choice: with the new findings, we have yet another option to help effectively manage patients with mild asthma.

CONFLICT OF INTEREST PMO is an advisory board member for AstraZeneca, Boehringer Ingelheim, and GSK. He has received honoraria for lectures for AstraZeneca, Boehringer Ingelheim, and Chiesi, and research grants from AstraZeneca, Medimmune and Novartis. FM has received honorary for lectures from Sandoz and for consultation from Chiesi.

REFERENCES

1 Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004; 59: 469-478.

2 GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017; 5: 691-706.

3 Demoly P, Gueron B, Annunziata K, et al. Update on asthma control in five European countries: results of a 2008 survey. Eur Respir Rev. 2010; 19: 150-157.

4 Braido F, Brusselle G, Guastalla D, et al. Determinants and impact of suboptimal asthma control in Europe: the international cross-sectional and longitudinal assessment on asthma control (LIAISON) study. Respir Res. 2016; 17: 51.

5 Dusser D, Montani D, Chanez P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy. 2007; 62: 591-604.

6 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Published 2018. Accessed September 17, 2018.

7 Pelaia G, Vatrella A, Busceti MT, et al. Cellular mechanisms underlying eosinophilic and neutrophilic airway inflammation in asthma. Mediators Inflamm. 2015; 2015: 879783.

8 Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. J Allergy Clin Immunol. 2001; 107: 937-944.

9 Adams NP, Bestall JB, Malouf R, et al. Inhaled beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev. 2005; 1: CD002738.

10 Adams NP, Bestall JC, Jones PW. Budesonide for chronic asthma in children and adults. Cochrane Database Syst Rev. 2001; 4: CD003274.

11 Adams NP, Bestall JC, Lasserson TJ, et al. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database Syst Rev. 2008; 4: CD003135.

12 Barnes PJ. Inhaled corticosteroids. Pharmaceuticals (Basel). 2010; 3: 514-540.

13 Demoly P, Annunziata K, Gubba E, Adamek L. Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years. Eur Respir Rev. 2012; 21: 66-74.

14 Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J. 2000; 16: 802-807.

15 Fletcher M, Jha A, Dunlop W, et al. Patient reported burden of asthma on resource use and productivity across 11 countries in Europe. Adv Ther. 2015; 32: 370-380.

16 Ko FW, Hui DS. Many patients labelled as having mild asthma do not have well-controlled asthma. Respirology. 2018; 23: 348-349.

17 Gillisen A. Patient's adherence in asthma. J Physiol Pharmacol. 2007; 58 (suppl 5): 205-222.

18 Adams RJ, Fuhlbrigge A, Guilbert T, et al. Inadequate use of asthma medication in the United States: results of the asthma in America national population survey. J Allergy Clin Immunol. 2002; 110: 58-64.

19 Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. Clin Chest Med. 2012; 33: 405-417.

20 Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. J Allergy Clin Immunol. 2006; 118: 899-904.

21 Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respir Care. 2015; 60: 455-468.

22 Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol. 2011; 128: 1185-1191.e2.

23 Rand C, Bilderback A, Schiller K, et al. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial. J Allergy Clin Immunol 2007; 119: 916-923.

24 Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014; 43: 343-373.

25 Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003; 361: 1071-1076.

26 Rabe KF, Atienza T, Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 2006; 368: 744-753.

27 O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005; 171: 129-136.

28 Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin. 2004; 20: 1403-1418.

29 Rabe KF, Atienza T, Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet. 2006; 368: 744-753.

30 Louis R, Joos G, Michils A, et al. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. Int J Clin Pract. 2009; 63: 1479-1488.

31 Bousquet J, Boulet LP, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007; 101: 2437-2446.

32 Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007; 61: 725-736.

33 O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med. 2005; 171: 129-136.

34 Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013; 12: CD009019.

35 Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013; 4: CD007313.

36 Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med. 2007; 356: 2040-2052.

37 Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. JAMA. 2012; 308: 987-997.

38 O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med. 2018; 378: 1865-1876.

39 Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med. 2018; 378: 1877-1887.